

Development of Circulatory-Renal Limitations to Angiotensin-Converting Enzyme Inhibitors Identifies Patients With Severe Heart Failure and Early Mortality

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OBJECTIVES	This study examined the hypothesis that patients who develop angiotensin-converting enzyme inhibitor intolerance attributable to circulatory-renal limitations (CRLimit) have more severe underlying disease and worse outcome.
BACKGROUND	Although the renin-angiotensin system contributes to the progression of heart failure (HF), it also supports the failing circulation. Patients with the most severe disease may not tolerate inhibition of this system.
METHODS	Consecutive inpatient admissions to the cardiomyopathy service of the Brigham and Women's Hospital between 2000 and 2002 were reviewed retrospectively for initial profiles, discharge medications, and documented reasons for discontinuation of angiotensin-converting enzyme inhibitors. Outcomes of death and transplantation were determined.
RESULTS	Of the 259 patients, 86 were not on an angiotensin-converting enzyme inhibitor at discharge. Circulatory-renal limitations of symptomatic hypotension, progressive renal dysfunction, or hyperkalemia were documented in 60 patients (23%); other adverse effects, including cough, in 24 patients; and absent reasons in 2 patients. Compared with patients on angiotensin-converting enzyme inhibitors, patients with CRLimit were older (60 vs. 55 years; $p = 0.006$), with longer history of HF (5 vs. 2 years; $p = 0.009$), lower systolic blood pressure (104 vs. 110 mm Hg; $p = 0.05$), lower sodium (135 vs. 138 mEq/L; $p = 0.002$), and higher initial creatinine (2.5 vs. 1.2 mg/dL; $p = 0.0001$). Mortality was 57% in patients with CRLimit and 22% in the patients on angiotensin-converting enzyme inhibitors during a median 8.5-month follow-up ($p = 0.0001$).
CONCLUSIONS	Development of CRLimit to angiotensin-converting enzyme inhibitor intolerance identifies patients with severe disease who are likely to die during the next year. New treatment strategies should be targeted to this population. (J Am Coll Cardiol 2003;41:2029-35) © 2003 by the American College of Cardiology Foundation

Angiotensin-converting enzyme inhibitors decrease disease progression and mortality from left ventricular dysfunction (1-5). Therapy with angiotensin-converting enzyme inhibitors is recommended for all patients with heart failure (HF) and reduced ejection fraction (6). The prevalence of angiotensin-converting enzyme inhibitor administration among patients with HF has been reported as 24% to 86% (7-14). Angiotensin-converting enzyme inhibitor intolerance is generally considered to be in the range of 8% to 15% (15-18). From large trials conducted after angiotensin-converting enzyme inhibitor therapy became standard practice, it has been estimated that 90% to 95% of such patients will be on angiotensin-converting enzyme inhibitors (19-21).

In normal circulation, the renin-angiotensin system supports blood pressure and renal perfusion via angiotensin-II mediated vasoconstriction in the periphery and efferent

renal arterioles, potentiation of sympathetic stimulation, and aldosterone release. Prolonged stimulation of this system contributes to deleterious cardiovascular remodeling that has been ameliorated by inhibition of components of the renin-angiotensin system. Despite these advances, HF remains a progressive disease. As circulation becomes increasingly impaired, the renin-angiotensin system may become indispensable for maintenance of blood pressure, renal perfusion, and glomerular filtration (22). Thus, the progression to more advanced HF may be characterized by development of a higher rate of angiotensin-converting enzyme inhibitor nonuse than seen in previous populations.

This study examines angiotensin-converting enzyme inhibitor discontinuation and outcomes among patients hospitalized with symptomatic HF and reduced ejection fraction, with hypotheses: 1) a lower rate of angiotensin-converting enzyme inhibitor prescription at discharge than current standards may occur in advanced HF, owing to circulatory-renal limitations (CRLimit) of symptomatic hypotension, progressive renal dysfunction, or hyperkalemia; and 2) patients previously on angiotensin-converting enzyme inhibitors in whom angiotensin-converting enzyme

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Manuscript received October 30, 2002; revised manuscript received January 17, 2003, accepted January 24, 2003.

Abbreviations and Acronyms

CRLimit	=	circulatory-renal limitations
HF	=	heart failure
LVAD	=	left ventricular assist device
NYHA	=	New York Heart Association
SBP	=	systolic blood pressure

inhibitors are discontinued because of circulatory or renal limitations have more severe underlying disease and worse outcome.

METHODS

Study population. The study population comprised consecutive patients followed by the Cardiomyopathy Service of the Brigham and Women's Hospital for whom HF discharge information was recorded between 2000 and 2002. For patients admitted more than once during this period, data from their most recent hospitalization were collected. Patients were excluded if the left ventricular ejection fraction was $>45\%$, or if death, cardiac transplantation, or placement of a permanent mechanical circulatory device occurred during hospitalization.

Data collection. Data were abstracted from hospital and outpatient medical records. Establishment of reasons for angiotensin-converting enzyme inhibitor nonuse relied exclusively on explicit written documentation in the progress notes of the reason for angiotensin-converting enzyme inhibitor nonuse. No assumptions were based on the patient's clinical status or laboratory data. Because all patients not on angiotensin-converting enzyme inhibitors at hospital discharge had undergone previous therapy with angiotensin-converting enzyme inhibitors either during or before hospitalization, the timing and location of angiotensin-converting enzyme inhibitor discontinuation were also recorded.

Demographic information, clinical characteristics during hospitalization, and therapies on discharge were collected. Baseline clinical descriptors included duration of HF by either symptoms or known reduced left ventricular ejection fraction, and New York Heart Association (NYHA) functional class before hospitalization (as noted in the ambulatory record by the outpatient cardiologist or in the admission note as the baseline functional status before the symptoms precipitating hospitalization). Heart rate and blood pressure were recorded on admission and discharge; electrocardiographic rhythm on admission; serum sodium concentration on admission, discharge, and the lowest value during hospitalization; and serum creatinine concentration on admission, discharge, and the highest value during hospitalization.

Follow-up. Death, cardiac transplantation, and placement of a left ventricular assist device (LVAD) at the Brigham and Women's Hospital were collected between January and April of 2002 with a median 8.5-month follow-up. To

ensure that deaths not occurring at the Brigham and Women's Hospital would be recorded, information was also collected from the Social Security Death Index. Approval for this study was obtained from the Institutional Review Board of the Brigham and Women's Hospital.

Determination of angiotensin-converting enzyme inhibitor use. Patients were divided into groups based on the presence or absence of an angiotensin-converting enzyme inhibitor among the medications prescribed at hospital discharge. Patients not receiving angiotensin-converting enzyme inhibitors at hospital discharge were then grouped on the basis of the reasons for nonuse as documented in the medical record: CRLimit (symptomatic hypotension, progressive renal insufficiency, or hyperkalemia), adverse effects (cough-other; all other reasons), and unable to be determined from the written record. Patients exhibiting side effects of both CRLimit and adverse effects were analyzed as part of the CRLimit group. The two patients with unknown reasons for angiotensin-converting enzyme inhibitor nonuse were excluded from the subsequent analysis.

Statistical analysis. Continuous variables were summarized by the median and quartiles and groups were compared using the Wilcoxon rank sum test. Categorical variables were summarized by proportions and compared using Fisher's exact test. Product-limit methods were used for time to event (death, cardiac transplantation, or LVAD placement), and groups were compared using the log-rank test. A multiple variable Cox proportional hazards model was developed to assess the impact of CRLimit relative to angiotensin-converting enzyme inhibitors for time to event after controlling for age, ejection fraction, presence of coronary artery disease, systolic blood pressure, sodium, and creatinine. The criterion for entry and removal was 0.10 and all selection methods resulted in the same final model. SAS/STAT software was used (version 8.2, SAS Institute Inc., Cary, North Carolina).

RESULTS

Study populations. Of the 316 patients followed, 57 patients were excluded because of ejection fraction $>45\%$, or end points during hospitalization. The remaining 259 patients comprise a population with advanced HF, evidenced by median ejection fraction of 22%, 59% with NYHA class III to IV HF at baseline before hospitalization.

Angiotensin-converting enzyme use and discontinuation. Of the 259 patients in the study population, 86 (33%) were not on an angiotensin-converting enzyme inhibitor at hospital discharge (Table 1). There were 60 patients with CRLimit to angiotensin-converting enzyme inhibitors (the CRLimit group), the majority with progressive renal insufficiency and symptomatic hypotension, and 24 with other effects (the cough-other group), primarily cough. Reasons for angiotensin-converting enzyme inhibitor nonuse were explicitly documented in the medical records for all except two patients, who were excluded from the subsequent

Table 1. Major Limitations to Angiotensin-Converting Enzyme Inhibitor Use

Reason for Intolerance	Percent (number*)
Adverse effect	
Cough	23.3 (20)
Taste disturbance	1.2 (1)
Angioedema	3.5 (3)
Hypereosinophilia	1.2 (1)
Circulatory-renal limitations	
Symptomatic hypotension	16.3 (14)
Renal insufficiency	45.3 (39)
Symptomatic hypotension and renal insufficiency	5.8 (5)
Hyperkalemia	2.3 (2)
Unknown	2.3 (2)

*Because one patient had both taste disturbance and hypotension, n = 87.

analysis. All of the remaining 84 patients had previously been on an angiotensin-converting enzyme inhibitor.

The angiotensin-converting enzyme inhibitor was discontinued during a prior hospitalization in 18 patients, in the course of outpatient treatment preceding hospitalization for 24 patients (12 by a primary care provider and 12 by an outpatient cardiologist), and during the current hospitalization for 32 patients. The location of angiotensin-converting enzyme inhibitor discontinuation was not available for 10 patients.

Baseline characteristics of patients with circulatory-renal limitations to angiotensin-converting enzyme inhibitors.

The CRLimit patients had more than twice the duration of known HF as patients still taking angiotensin-converting enzyme inhibitors (5 vs. 2 years, $p < 0.009$). The preadmission clinical class was III or IV in 82%, versus only 50% in patients discharged on angiotensin-converting enzyme inhibitors. Other clinical descriptors of worse outcome in this population included older age and higher prevalence of ischemic etiology (Table 2). The CRLimit patients did not

differ significantly from the patients on angiotensin-converting enzyme inhibitors in gender, race, left ventricular ejection fraction, or prevalence of diabetes mellitus.

The systolic blood pressure on admission was 110 mm Hg in patients on angiotensin-converting enzyme inhibitors and 104 mm Hg in the CRLimit group ($p = 0.05$). The systolic blood pressure on discharge was 100 mm Hg in the patients still on angiotensin-converting enzyme inhibitors and 102 mm Hg in the CRLimit patients, 32 of whom had their angiotensin-converting enzyme inhibitors discontinued between admission and discharge. The admission and discharge creatinine were 1.2 mg/dl in the patients on angiotensin-converting enzyme inhibitors. In the CRLimit group, creatinine was 2.45 mg/dl at admission and 2.0 mg/dl at discharge. Of patients discharged on angiotensin-converting enzyme inhibitors, 41% had an initial creatinine >1.2 mg/dl, compared with 81% of the CRLimit patients. The highest recorded creatinine during hospitalization was 1.5 mg/dl in the patients on angiotensin-converting enzyme inhibitor and 3.0 mg/dl in the CRLimit group (all differences p value < 0.0001). The admission sodium was 138 mmol/l in the patients on angiotensin-converting enzyme inhibitors and 135 mmol/l in the CRLimit group ($p = 0.002$). The lowest recorded sodium during hospitalization was 135 mmol/l in the patients on angiotensin-converting enzyme inhibitors and 132 mmol/l in the CRLimit group ($p = 0.002$). The discharge sodium concentration was 138 mmol/l in patients on angiotensin-converting enzyme inhibitors and 136.5 mmol/l in patients with CRLimit ($p = 0.15$).

The discharge potassium was 4.2 mEq/l in the patients on angiotensin-converting enzyme inhibitors and 4.1 mEq/l in the CRLimit group ($p = 0.28$). The highest recorded potassium during hospitalization was 4.8 mmol/l in patients on angiotensin-converting enzyme inhibitors and 5.1

Table 2. Baseline Characteristics of Patients With Heart Failure Treated With and Without ACEIs

Baseline Characteristic	Percent of Patients or Median (25th to 75th Percentiles)			p Value (On ACEI vs. CRLimit)
	On ACEI (n = 173)	CRLimit (n = 60)	Cough-Other* (n = 24)	
Age (yrs)	55 (42–65)	60 (53–68)	64 (55–72)*	0.006
Male	70	80	37	0.18
African American	13%	5%	8%	0.14
Ischemic cardiomyopathy	43	65.0	50.0	0.004
Duration of heart failure (yrs)	2 (0.5–7)	5 (2–8)	3.5 (2–10)*	0.009
Ejection fraction (%)	22.5 (15–28)	20 (15–26.3)	20 (15–29)	0.45
NYHA class III to IV	50	82	67	0.00002
Diabetes mellitus	34	38	29	0.64
Systolic blood pressure (mm Hg)	110 (100–123)	103.5 (90–122)	105 (92–127)	0.05
Paced ECG rhythm	12	28	13	0.03
Creatinine (mg/dl)	1.2 (1.0–1.5)	2.5 (1.8–3.2)	1.4 (1.1–2.0)	0.0001
Sodium (mmol/l)	138 (136–140)	135 (130–139)	138 (136–140)	0.002
Potassium (mmol/l)	4.2 (3.9–4.5)	4.1 (3.7–4.5)	4.0 (3.7–4.3)	0.28

*Compared with patients on ACEI, the No ACEI-due to cough/other adverse effects were significantly older with intermediate duration of heart failure.

ACEI = angiotensin-converting enzyme inhibitors; CRLimit = circulatory-renal limitations; ECG = electrocardiogram; NYHA = New York Heart Association.

Table 3. Discharge Medications in Relation to ACEI Use or CRLimit

Discharge Medication	Percent of Patients or Median (25th to 75th Percentiles)		p Value
	On ACE (n = 173)	CRLimit (n = 60)	
Beta-blockers	50	25	0.0009
Loop diuretics (% of patients)	89	93	0.45
Furosemide dose (mg; n = 156)	160 (100–160)	160 (120–160)	0.28
Torsemide dose (mg; n = 53)	200 (100–200)	200 (100–400)	0.21
Thiazide diuretics	7	23	0.001
Nitrates	48	68	0.007
Hydralazine	4	43	0.0001
Spironolactone	26	33	0.32
Digoxin	62	43	0.01
Intravenous inotropes	0	23	0.0001

Abbreviations as in Table 2.

mmol/l in patients with CRLimit ($p = 0.12$). The two patients with history of hyperkalemia had peak potassium levels of 5.6 and 8.3 mEq/l documented during this hospitalization.

Discharge therapies. Compared with patients on angiotensin-converting enzyme inhibitors, half as many CRLimit patients were on beta-blockers, and almost four times as many were receiving thiazide diuretics in addition to loop diuretics at discharge (Table 3). One-quarter of the CRLimit group was discharged on home intravenous inotropic therapy. The median daily dose of loop diuretics was similarly high in both groups.

The cough-other group. The relatively small group with other side effects limiting angiotensin-converting enzyme inhibitors (cough-other group, $n = 24$) resembled the patients on angiotensin-converting enzyme inhibitors in most clinical characteristics (Table 1). The cough-other patients were significantly older than patients on angiotensin-converting enzyme inhibitors and 62.5% were women. The cough-other group had similar use of beta-blockers, and no patients were discharged on home intravenous inotropic infusions. Angiotensin-receptor blocker use was 75%.

Survival. During a median 8.5-month follow-up, death occurred in 22% of patients on angiotensin-converting enzyme inhibitors and 57% of the CRLimit patients ($p = 0.0001$). The rate of heart transplantation was 4.6% in the patients on angiotensin-converting enzyme inhibitors and 6.7% in the CRLimit group ($p = 0.51$), with rates of LVAD placement 2.3% and 3.3%. The combined event rate (death, heart transplantation, or LVAD placement) was 27% in patients on angiotensin-converting enzyme inhibitors and 62% in the CRLimit patients ($p = 0.0001$). Subsequent analyses are for the combined end point of death, heart transplantation, and LVAD placement. The estimated proportion of patients without an event at six

months was $82 \pm 3\%$ for patients on angiotensin-converting enzyme inhibitors and $44 \pm 7\%$ for the CRLimit patients ($p < 0.0001$; Fig. 1). The increased event rate in the CRLimit patients is evident by the end of the first month.

Of the 60 patients in the CRLimit group, 14 were discharged on intravenous inotropic therapy. The combined event rate was 86% in CRLimit patients discharged on IV inotropic therapy and 54% in CRLimit not on IV inotropic therapy ($p = 0.0002$).

The combined event rate for the cough-other group was 45.8% ($p = 0.0001$ compared with patients on angiotensin-converting enzyme inhibitors). The estimated proportion of patients without an event at six months was $55 \pm 11\%$ ($p = 0.006$ compared with patients on angiotensin-converting enzyme inhibitors).

A multiple variable proportional hazards model was developed to assess the risk of having an event for CRLimit relative to angiotensin-converting enzyme inhibitors while controlling for potentially confounding factors known to influence outcome: age, ejection fraction, ischemic cardiomyopathy, systolic blood pressure, creatinine, and sodium (23–32). The final parsimonious model retained sodium, systolic blood pressure, and age in addition to the angiotensin-converting enzyme inhibitor grouping. The hazard ratio for CRLimit relative to angiotensin-converting enzyme inhibitors while controlling for these factors was 2.8 (95% confidence interval [1.8, 4.4], $p = 0.0001$).

DISCUSSION

This study demonstrates that 33% of patients hospitalized on a HF referral service were discharged without prescription of angiotensin-converting enzyme inhibitor therapy, with documentation of reasons for non-angiotensin-converting enzyme inhibitor use after prior angiotensin-converting enzyme inhibitor therapy explicitly available in all but 2% of patients. The 23% of patients who developed CRLimit to angiotensin-converting enzyme inhibitor use had more advanced disease in duration and symptom severity, with lower blood pressure and serum sodium, and worse renal function, when compared with patients still taking angiotensin-converting enzyme inhibitors or the smaller group not taking angiotensin-converting enzyme inhibitors because of angioedema or intolerable cough. The development of perceived CRLimit to angiotensin-converting enzyme inhibitors identified a population with high early mortality.

Evolution of population with limitations to angiotensin-converting enzyme inhibitor use. Many studies have investigated the rates of angiotensin-converting enzyme inhibitor administration in patients with HF (7–14). Early studies noted that 24% to 86% of patients with left ventricular systolic dysfunction were on angiotensin-converting enzyme inhibitors, with low rates attributed to delayed penetration of guidelines regarding angiotensin-converting enzyme inhibitor therapy into practice. In the mid 1990s,

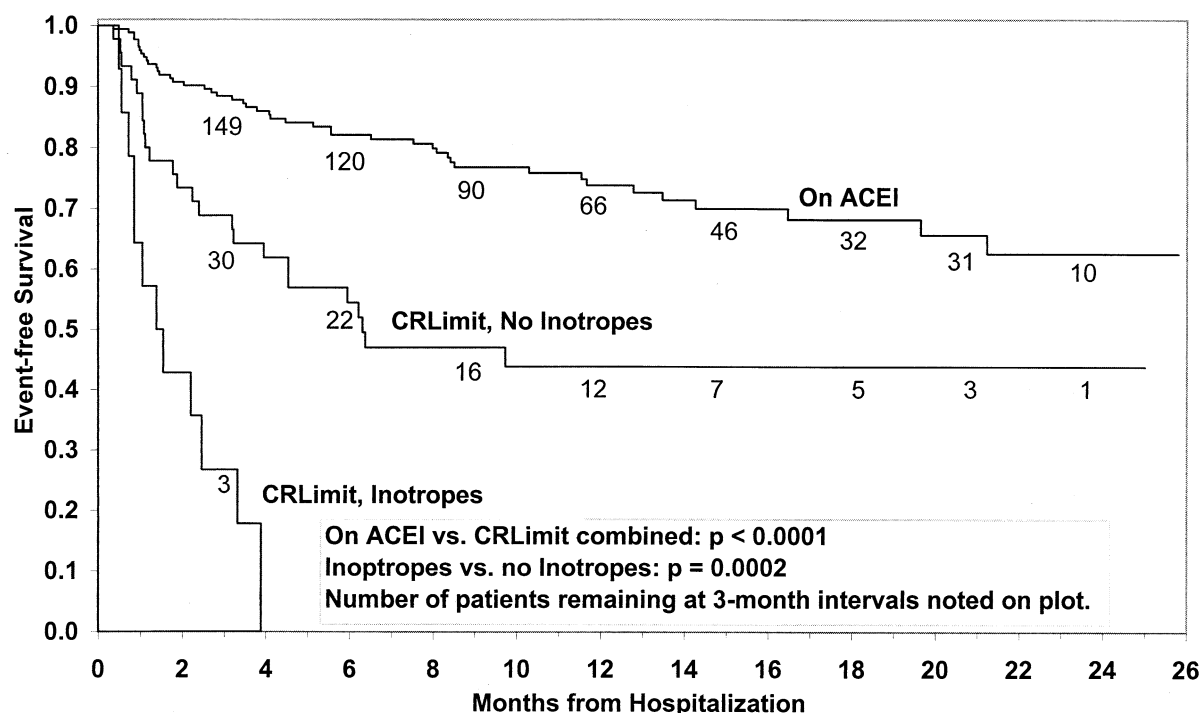


Figure 1. Kaplan-Meier plot of survival without left ventricular assist device or transplant for 173 patients on angiotensin-converting enzyme inhibitors (ACEI), 45 patients with circulatory-renal limitations (CRLimit) not on intravenous (IV) inotropes, and 14 patients with CRLimit on IV inotropes. Patients on angiotensin-converting enzyme inhibitors had significantly longer survival time than patients with CRLimit ($p < 0.0001$). CRLimit patients who did not receive IV inotropes had significantly longer survival times than CRLimit patients who received IV inotropes ($p = 0.002$). The numbers of patients remaining at three-month intervals up to 24 months are noted on the plot.

the SPICE registry examined 9,280 patients from North American and European sites (33). Angiotensin-converting enzyme inhibitors were not prescribed in 20% of patients, because of cough or angioedema in 9.4% of patients and possible circulatory or renal limitations in 9% of patients. Bart *et al.* (34) examined data from a similar period and found that of 242 patients admitted to a tertiary care medical center with HF, 24% were not on angiotensin-converting enzyme inhibitors, among whom 42.1% exhibited circulatory or renal limitations. The lower prevalence of angiotensin-converting enzyme inhibitor nonuse and the lower rate of CRLimit in these studies may reflect lower disease acuity in their population, in which the ejection fraction was 27% compared with 22% in this study, and only 9% of their population had NYHA class IV HF at baseline. The current demonstration of the higher rate of 33% not taking angiotensin-converting enzyme inhibitors is in patients with more advanced HF. In this study, beginning after 2000, all patients had previously been tried on angiotensin-converting enzyme inhibitors, and the reason for non-angiotensin-converting enzyme inhibitor use was documented in 98% of patients. Compared with spontaneous documentation in only 65% in the earlier study from eight years ago, the higher rate may reflect a heightened awareness of both the trials of angiotensin-converting enzyme inhibitor therapy and potential scrutiny of prescribing performance.

Characterization of patients with CRLimit to angiotensin-converting enzyme inhibitors. The phenomenon of CRLimit to angiotensin-converting enzyme inhibitor use is becoming more obvious as the experience with HF lengthens. These patients had an average disease duration of five years, compared with two years in patients still tolerating angiotensin-converting enzyme inhibitors. The success of early therapy to delay disease progression and prevent untimely sudden death is allowing more patients to advance to the stage of disease beyond current therapies and guidelines. In addition to the longer duration of disease, patients with CRLimit to angiotensin-converting enzyme inhibitor use demonstrated other baseline characteristics of greater disease severity. These patients had almost triple the incidence of class IIIB to IV HF symptoms characterized before the events leading to hospitalization, with higher mortality expected (23). Renal insufficiency with or without symptomatic hypotension accounted for the most common CRLimit, and higher creatinine has recently been shown in multiple studies to be a very strong predictor of worse outcome, even for modest elevations (24–27). Long recognized to be a predictor of worse outcome, low serum sodium has also been described previously as associated with greater limitation to angiotensin-converting enzyme inhibitor initiation (29). The other major limitation of angiotensin-converting enzyme inhibitor use, symptomatic hypotension, reflects lower systolic blood pressure, a robust predictor of

worse outcome in recent trials in which it has been reported (29,30).

Other baseline factors predicting higher risk in the population with circulatory renal limitations to angiotensin-converting enzyme inhibitor use are greater age (30) and a higher incidence of ischemic cardiomyopathy (31). Left ventricular ejection fraction was not different, and has not been a strong predictor once severely reduced (32). Paced rhythm has been associated with progression of hemodynamic decompensation, and was twice as common in the CRLimit group (35).

The discharge therapies of the CRLimit patients are also consistent with an unstable population of advanced HF. The lower rate of beta-blocker use confirms either the perception or recognition of inability to tolerate inhibition of the sympathetic nervous system. The high median daily dose of loop diuretics and a higher rate of thiazide diuretic use imply more refractory fluid retention. The most important medication difference may be the frequency, previously unappreciated at the investigating center, of intravenous inotropic infusions to allow discharge of 23% of patients unable to tolerate angiotensin-converting enzyme inhibitors. Because intravenous inotropic therapy is generally continued only to support blood pressure for ambulation or renal function to relieve congestive symptoms, it was not used in any patients able to tolerate angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, as the program policy was to try all other options, including discontinuation of these agents, before accepting inotropic dependence.

Outcomes of patients with CRLimit to angiotensin-converting enzyme inhibitors. Despite mean follow-up of only 8.5 months, the CRLimit patients demonstrated an almost 2.5-fold higher incidence of death, ventricular assist device placement, and transplantation. Whereas angiotensin-converting enzyme inhibitor intolerance may have influenced decisions regarding mechanical support and transplantation, these accounted for only six of the 37 events. Multiple factors may contribute to the >50% mortality of the angiotensin-converting enzyme inhibitor group within six months. Baseline characteristics would have predicted that the CRLimit group would have mortality in excess of the patients on angiotensin-converting enzyme inhibitors, regardless of treatment. To the extent possible with this limited population, multivariate analysis supports an independent contribution of the descriptor of CRLimit to higher mortality, even when adjusting for age, presence of coronary artery disease, ejection fraction, systolic blood pressure, sodium, and creatinine. In ways only partly reflected by previous predictors, these patients may not tolerate angiotensin-converting enzyme inhibitors because of more severe underlying cardiac and renal compromise, leading to greater dependence on the renin-angiotensin system for immediate support of blood pressure and renal perfusion.

The absence of benefit from angiotensin-converting en-

zyme inhibitor therapy itself may contribute to higher mortality. The mortality for patients with idiosyncratic rather than CRLimit to angiotensin-converting enzyme inhibitors was higher than for patients on angiotensin-converting enzyme inhibitors, suggesting adverse impact of a non-angiotensin-converting enzyme inhibitor regimen, even with the prescription of angiotensin-II antagonists in most of these patients. The nature and degree of circulatory and renal contraindications to angiotensin-converting enzyme inhibitor use are controversial. All patients had previously been receiving chronic angiotensin-converting enzyme inhibitor therapy. The strong commitment to angiotensin-converting enzyme inhibitor use by the HF care team in this study led to repeated attempts to use angiotensin-converting enzyme inhibitors by modifying other components of the regimen. However, without rigid prospective definitions, it is not possible to determine whether other solutions could be found without discontinuing angiotensin-converting enzyme inhibitors. Survival might have been improved if angiotensin-converting enzyme inhibitors were continued with less physician concern for symptomatic hypotension, or if patients were maintained on angiotensin-converting enzyme inhibitors at the cost of a higher volume status with increased congestive symptoms but more stable renal function. These decisions require individualization of priorities, which for some patients favor symptom relief over survival when severe symptoms limit comfort at rest.

The use of chronic outpatient inotropic therapy in 23% of the CRLimit patients itself was a likely factor in the increased mortality of the overall CRLimit group. Mortality in patients receiving continuous intravenous inotropic agents has been reported as 30% to 50% by six months, as observed in this study (29).

Study limitations. Because this study focuses on patients treated at a center specializing in HF, the results may not reflect those of routine clinical practice. However, this is the ideal population in which to begin study of the CRLimit population because of the familiarity of HF/transplant referral programs with the importance of angiotensin-converting enzyme inhibitors and with the low blood pressures and renal dysfunction in the more advanced stages of disease. Because angiotensin-converting enzyme inhibitor titration and documentation were not performed in anticipation of this review, there was no standard definition among differing HF physicians, but there was thus an opportunity to determine the adequacy of routine spontaneous documentation. This study had only 8.5 months of mean follow-up. Nevertheless, even in this short time period, >50% of the CRLimit patients had died.

Conclusions. Patients hospitalized with advanced HF who are discharged without angiotensin-converting enzyme inhibitors because of perceived CRLimit have >50% six-month mortality that may reflect not only greater duration and severity of HF, but also the paucity of information regarding best therapy. Greater recognition and focus on

therapies for the population of patients with CRLimit to angiotensin-converting enzyme inhibitor use are critical as the duration of HF survival increases and more patients face these limitations.

Acknowledgment

Statistical analyses were supported in part by the Biostatistics Consulting Service, Center for Clinical Investigation, Brigham and Women's Hospital.

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